UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,691	11/12/2003	Andrew Robert Davids	674582-2001	5783

20999 7590 06/06/2007

FROMMER LAWRENCE & HAUG
745 FIFTH AVENUE- 10TH FL.
NEW YORK, NY 10151

EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
06/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,691	DAVIDS ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-15 and 17-79* is/are pending in the application.

4a) Of the above claim(s) *4-9,17-19,22-77 and 79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10-15,20,21,78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The previous Office Action of 27 December 2006 is hereby vacated. New Office Action is set forth below.

Status of Application, Amendments, And/Or Claims:

The amendment received 13 April 2006 in response to the Office Action of 23 November 2005 has been entered. Claims 1, 4-15, and 17-79 are pending in the instant application. Claims 2, 3, and 16 have been cancelled. Claims 1, 10-13, 15 and 20 have been amended and the amendments made of record. New claims 78 and 79 have been submitted and entered.

The Office Communication of 6 September 2006 stated that the inclusion of SEQ ID NOs:4 and 6 in claims 1 and 79, which were not recited in the claims as originally presented would require new searches of the databases. Applicants traverse this assertion in remarks of 6 October 2006. The reason for the traversal is that the inventors teach that SEQ ID Nos:4 and 6 are fragments of SEQ ID NO:16, and thus a proper search would have included SEQ ID NOs:4 and 6. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. The search of the polypeptide of SEQ ID NO:16 would not reveal sequences identical to the fragments of SEQ ID NOs:4 and 6. The search of SEQ ID NO:16 would look for identity over the full length of the molecule rather than match particular fragments. Separate, new searches of fragments of SEQ ID NOs:4 and 6 would be required and given the amount of computer time required, would be unduly burdensome.

Claims 1, 10-15, 20, 21 and 78 are under consideration to the extent they read on originally examined sequences of SEQ ID NOs 16, 20, 22 and 26. **This new office action addresses Claim 1 (iii) a fusion protein comprising a polypeptide according to Claim i) or ii) fused to a heterologous polypeptide and New claim 78 draw to an isolated polypeptide according to claim 1 (iii) which comprises or consists of the amino acid sequence as recited in SEQ ID NO:20 or in SEQ ID**

NO:22 fused to a heterologous polypeptide. Claims 4-9, 17-19, 22-77 and 79 are withdrawn from consideration as directed to non-elected inventions.

Please see previous, now vacated Office Action for any Art not cited on 892 included herein.

Information Disclosure:

The IDS submitted on 23 March 2006 has been considered and made of record. It appears that two identical IDS's were submitted at the same time. The references on one of them have been crossed out and not considered, as they are duplicates of ones submitted on page 1 of the IDS.

Withdrawn Objections/Rejections

The objection to the claim 15 as containing non-elected subject matter is withdrawn in view of Applicants' amendment to the claim.

All rejections of claims 2, 3 and 16 are withdrawn. Applicants have cancelled the claims thereby rendering all rejections moot.

The rejection of Claims 1, 10, 11, and 15 under 35 U.S.C. 101 because the claims read on a product found in nature is withdrawn in view of Applicants' amendments to the claims.

The rejection of Claims 1, 10-15, 20 and 21under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reciting the phrases "antigenic determinant" and "increases or decreases the level of expression or activity of a polypeptide" is withdrawn in view of applicants amendments to the claims.

The rejection of Claims 1, 11-13, and 15 under 35 U.S.C. 112, first paragraph for failing to comply with the enablement and written description requirement is withdrawn, in view of applicants' amendments to the claims.

The rejection of Claims 1 and 12-14 under 35 U.S.C. 102(b) as being anticipated by Edwards, et al. (US 6,783,961) is withdrawn in view of applicants' amendments to the claims.

Maintained/New Rejections and/or Objections

Objections:

Claim 1 is objected to as being drawn to non-elected subject matter. The claim recites non-elected sequences. Appropriate correction is required.

Claim 78 is objected to because of the following informalities: there is a misspelling in the claim. "Heterlogous" is a misspelling of the word "heterologous". Appropriate correction is required.

35 U.S.C. § 112, Second Paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 10-15, 20, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1(iv) recites "characterized in that it is homologous to the amino acid sequence as recited.....". The claim is vague and indefinite in that the claim is drawn to molecules of unspecified homology to the amino acid sequence as recited in SEQ ID NOs:16 and 26. Therefore, the metes and bounds of the claim cannot be determined.

Additionally, it is unclear if the phrase "has activity as an antagonist of cytokine expression and/or secretion" applies to all parts of claim 1, or only to part iv.

Claims 10-15, 20 and 21 are included in this rejection as dependent upon a rejected claim.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,10-15, 20, 21 and 78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a full length polypeptide comprising or consisting of SEQ ID NOs:16, 20, 22 or 26 or a fusion polypeptide comprising a polypeptide which comprises or consists of the amino acid sequence as recited in SEQ ID NOs:16, 20, 22 or 26 fused to a heterologous polypeptide that has an activity that is an antagonist of TNF-alpha, IL-4, IL-6 and or IL-2 does not reasonably provide enablement for a full length polypeptide or a fusion protein or a fusion protein comprising a fragment of a polypeptide (SEQ ID NOs:16, 20, 22 or 26) that has an activity that is an antagonist to any cytokine expression and/or secretion or a functional equivalent of a polypeptide comprising the amino acid sequence of SEQ ID NOs: 16, 26, 20 or 22 that has an activity that is an antagonist to any cytokine expression and/or secretion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention and the claims: The invention is drawn to isolated polypeptides of SEQ ID NOs:16 (INSP052), 20 (extracellular domain of INSP052), 22 (extracellular domain of mature INSP052 polypeptide) or 26 (mature INSP052

polypeptide), or fusion proteins comprising or consisting of SEQ ID NOs: 16, 20, 22, or 26 or fragment thereof fused to a heterologous polypeptide or functional equivalents that are homologous to the amino acid sequences of SEQ ID NOs:16, 20, 22 or 26. Thus, the claims are broadly drawn to polypeptides which are functional equivalents that have undisclosed homology to the amino acid sequences of SEQ ID NOs:16, 20, 22 or 26 and fusion proteins comprising fragments of SEQ ID NOs:16, 20, 22 or 26 fused to heterologous polypeptides and which have activity as an antagonist of any cytokine expression and/or secretion.

The specification discloses:

With respect to functionally equivalent polypeptides:

The functionally-equivalent polypeptides of the of the invention may be polypeptides that are homologous to the INSP052 ...polypeptides, preferably the INSP052 extracellular domain (i.e. SEQ ID NO:20 or SEQ ID NO:22). Typically, greater than 30% identity between two polypeptides is considered to be an indication of functional equivalence [paragraph 0107 in USPGPUB 20040204352, the PGPUB of the instant application]. Two polypeptides are said to be "homologous", as the term is used herein, if the sequence of one of the polypeptides has a high enough degree of identity or similarity to the sequence of the other polypeptide [paragraph 0097]. Homologous polypeptides include natural biological variants (for example, allelic variants or geographical variations within the species from which the polypeptides are derived) and mutants (such as mutants containing amino acid substitutions, insertions or deletions) of the INSP052 peptide ..... preferably of the INSP052 extracellular domain. [paragraph 0106]. However, the specification does not disclose the structures that are important for retention of polypeptide activity. The specification fails to provide any guidance as to how to produce homologous proteins (of unspecified homology) which retain the recited biological activity, that of a cytokine antagonist. The claims, as presented, read on any molecule that would have the function of a cytokine antagonist.

With respect to fusion proteins comprising fragments of polypeptides:

There is no guidance presented in the specification as to how to make and/or use fusion proteins comprising fragments of SEQ ID NOs:16, 20, 22 or 26 fused to

heterologous polypeptides. There is no teaching as to which domains of the molecules must be conserved in the fusion proteins in order to retain the function of a cytokine antagonist.

With respect to antagonist activity:

The polypeptides of the instant invention have activity as a cytokine antagonist, particularly as an antagonist of cytokine expression and/or secretion, particularly with respect to TNF-alpha, IL-4 and/or IL-2. The specification teaches that the extracellular domain of INSP052 (also referred to herein as INSP052EC) downregulates TNF-alpha, IL-4 and IL-2 secretion *in vitro* in a Concanavalin A (ConA) stimulated human peripheral blood mononuclear cells (hPBMC) assay. Delivery of INSP052EC cDNA in an *in vivo* model of fulminant hepatitis (animals treated with ConA) decreases TNF-alpha and m-IL-6 levels in serum of treated animals [paragraph 0026, 0027]. Thus, Applicants envision that the polypeptides of the instant invention are inhibitory of pro-inflammatory cytokines. There are no teachings as to the effect of the polypeptides of the instant invention of expression or secretion of any of the myriad of other cytokines.

The working models (Examples 4 and 5) are limited to assays which measure the effects of full length INSP052EC on cytokine secretion *in vitro* and *in vivo* in a mouse model of Concanavalin A (ConA)-induced liver hepatitis. INSP052EC downregulated the secretion of TNF-alpha, IL-4 and IL-2 secretion form Con-A-stimulated hPBMC (example 4). INSP052EC-electrotransferred animals show reduction in TNF-alpha and IL-6 cytokine levels after ConA treatment. There are no working or prophetic examples directed to effects of homologous proteins, fusion proteins, fusion proteins comprising fragments of the recited sequences or to the effects of INSP052 proteins on the expression and/or secretion of any other cytokines.

The art teaches with respect to homologous proteins:

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein with the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of

success are limited. Certain positions in the sequences are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al, 1990, *Science* 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, *Biochemistry* 29:8509-8517; Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, Merz et al., eds, Birkhauser, Boston, pp. 491-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active protein variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible homologues of proteins of SEQ ID NOs:16, 20, 22 or 26 or of fusion proteins comprising fragments of SEQ ID NOs:16, 20, 22 or 26. Neither the specification nor the state of the art teaches one skilled in the art if any homologue of a protein of SEQ ID NOs:16, 20, 22 or 26 or fusion protein comprising fragment of SEQ ID NOs:16, 20, 22 or 26 would possess the same biological activity compared to the full-length polypeptide or fusion protein comprising the full-length polypeptide.

Therefore, based on the discussions above concerning the art's teaching which establishes the unpredictability of the effects of substitution, deletion and/or insertion of

even a single amino acid residue on protein structure and function, the disclosure in the specification that greater than 30% identity between two polypeptides is considered to be an indication of functional equivalence and that homologous polypeptides include natural biological variants and mutants, one of ordinary skill in the art would have to undertake undue experimentation to make and use the invention commensurate in scope with these claims.

Applicants' traverse the rejection set forth in the previous office (in response of 13 April 2006, page 14-15). The reasons for the transversal are:

a. the specification provides guidance how to make and use fragments and/or homologues that retain the cytokine antagonist function of the full length polypeptide by utilizing the Inpharmatica Gene Threader. Applicants assert that this system is not comparable (i.e. is superior) to basic tools previously known in the art.

b. examples in the application provide one with details of cytokine antagonist assays.

c. application teaches the functional importance of the immunoglobulin domain.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons.

The Inpharmatica Gene Threader system is acknowledged by applicants as being an in-house system developed by Inpharmatica (page 15 of response of 13 April 2006). This system did not appear to be publicly available at the time of filing of the instant invention. Therefore, one of ordinary skill in the art could not rely upon the Gene Threader system, in addition to guidance in the specification, or the teachings in the art to make and use fragments and/or homologues that retain the cytokine antagonist function of the full length polypeptide.

More importantly, the fact that there are art-recognized procedures to screen for cytokine-antagonist activity is not in dispute. As discussed above, neither the specification nor the art provide sufficient guidance as to the nature of active derivatives that may be constructed: homologues of full-length polypeptides that would retain cytokine antagonist activity or fusion proteins comprising fragments of full-length

polypeptide. Further, there is no conception of what might be found by doing so. Thus, one of skill in the art would have to undertake undue experimentation to make and use such homologous polypeptides or fusion proteins comprising fragments of SEQ ID NOs:16, 20, 22 or 26 before testing for cytokine antagonist activity.

Applicant teaches that the immunoglobulin domain is important for the biological activity. However, as discussed above, the immunoglobulin domain must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible homologues of proteins of SEQ ID NOs:16, 20, 22 or 26, since the percent homology is undefined nor do they disclose any actual or prophetic examples on expected performance parameters of any of the possible fusion proteins comprising fragments of SEQ ID NOs:16, 20, 22 or 26, since the portions of the full-length proteins which must be retained are not disclosed.

The art teaches with regard to cytokines:

Cytokines are regulatory proteins secreted by white blood cells and a variety of other cells in the body; the pleitropic actions of cytokines include numerous effects on cells of the immune system and modulation of inflammatory responses (Vilcek 2003. in Chapter 1, The Cytokine Handbook, 4th edition, page 5, 2nd column, 3rd paragraph). Individual cytokines tend to exert a multitude of actions on different cells and tissues. Some cytokines, such as TNF-alpha, IL-6, IL-2 and IL-4 are considered pro-inflammatory cytokines; others, such as IL-10, and IL-1 are considered to have anti-inflammatory effects. Thus, one would not wish to utilize the polypeptides of the instant invention to inhibit the expression and/or secretion of pro-inflammatory cytokines if applicants envision that the polypeptides of the instant envision have utility in treating inflammatory diseases.

Applicants' claims are excessively broad due to the complex and pleitropic nature of cytokine activities. Therefore, based on the discussions above concerning the art's recognition that generic cytokines have multiple effects, some cytokines being pro-

inflammatory, while others are anti-inflammatiory, the specification fails to teach the skilled artisan how to use the claimed methods without resorting to undue experimentation to determine which cytokines may be antagonized by the peptides of the instant invention.

Claims 15, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide or a fusion protein comprising a full length polypeptide for use in therapy for treatment of fulminant hepatitis in a mouse model does not reasonably provide enablement for a polypeptide or fusion protein comprising a full length polypeptide for use in therapy and diagnosis in an inflammatory disease, an autoimmune disease, any generic liver disease or liver failure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broadly drawn to polypeptides for use in therapy or diagnosis of any inflammatory disease, any autoimmune disease, any liver disease or liver failure of any etiology. Thus, therapeutic administration is encompassed within the claimed invention.

The specification discloses that the extracellular domain of INSP052 (also referred to herein as INSP052EC) downregulates TNF-alpha, IL-4 and IL-2 secretion *in vitro* in a Concanavalin A (ConA) stimulated human peripheral blood mononuclear cells (hPBMC) assay. Delivery of INSP052EC cDNA in an *in vivo* model of fulminant hepatitis (animals treated with ConA) decreases TNF-alpha and m-IL-6 levels in serum of treated animals [paragraph 0026, 0027]. Based on these results, applicants assert that INSP052, INSP052EC (SEQ ID NO.20 and SEQ ID NO.22) and related functionally equivalent proteins will be useful in treating auto-immune, viral or acute liver diseases as well as alcoholic liver failures and envision that these peptides are likely also to be effective in treating other inflammatory diseases [paragraph 0028]. The specification also teaches that polypeptides of the present invention or their immunogenic fragments (comprising at least one antigenic determinant) can be used to generate antibodies that

may be employed as diagnostic or therapeutic aids [paragraph 0112]. The specification teaches diseases may be diagnosed by methods comprising determining, from a sample derived from a subject, an abnormally decreased or increased level of polypeptide of instant invention or mRNA [paragraph 0253]. However, the specification does not disclose a nexus between levels of polypeptides of SEQ ID NOs:16, 20, 22, or 26 or increases or decreases in level of expression or activity of polypeptides of SEQ ID NOs:16, 20, 22, or 26 and any pathology or auto-immune or inflammatory disease, or liver diseases. Thus one of skill in the art would be unable to use the peptides of the claimed invention to diagnose any disease or pathology. The only teaching in the specification is that the expression of INSP052EC (SEQ ID NO.20 and SEQ ID NO.22) down regulates the expression of TNF-alpha and m-IL-6 levels in serum of animals with ConA-induced hepatitis, and decreases the levels of aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) in the serum of said animals. There are no other teachings in the disclosure of a relationship between the polypeptides of the instant invention and auto-immune or inflammatory disease, or naturally occurring liver diseases.

The working model: (Example 5) discloses INSP052EC-electrotransferred animals show reduction in TNF-alpha and IL-6 cytokine levels after ConA treatment. These animals also exhibit a decrease in ASAT and ALAT levels eight hours after ConA injections. There are no working or prophetic examples directed to the effects of INSP052 proteins on any naturally liver disease, or inflammatory disease, autoimmune disease or liver failure.

The art teaches: The art teaches that the etiology and pathology of the recited diseases is varied and not necessarily due to altered cytokine levels, or to alterations in just the levels of TNF-alpha and IL-6. For example, some liver diseases, such as the hereditary hepatic porphyrias are due to marked deficiencies of enzymes in the heme biosynthetic pathway (Nordmann et al. 2002. Clinica Chimica Acta 325:17-37, abstract). One would not predict that the polypeptides of the instant invention would be able to diagnose or treat the symptoms of this type of liver disease. Batey et al (2002. Frontiers in Bioscience 7:1662-1675) teach the role of IL-6 in alcohol hepatitis is still

unclear and may have a prophylactic effect against ConA-induced liver injury in mice, the working model of the instant invention (page 1665, 1st column, 2nd paragraph). Thus, one would not be able to predict that inhibiting expression and/or secretion of IL-6 would have a therapeutic effect even on Con-A induced liver disease. Moreover, the reference teaches that in both humans and experimental animals, chronic alcohol consumption affects cell-mediated immunity and humoral immunity. Thus, one sees an increase in IL-12, interferon-gamma, IL-4 and IL-10 cytokines in these subjects. Chronic ethanol consumption downregulates IL-12. In heavy drinkers, the defective secretion of IL-10, or IL-12 in relation to the regulation of pro-inflammatory cytokine production may be linked to the development of alcohol hepatitis (page 1664, 1st column, 3rd paragraph). Thus, it would be unpredictable that inhibition of levels of TNF-alpha and IL-6 by administration of the peptides of the instant invention would have a therapeutic effect on any liver disease or liver failure.

Applicants' claims are excessively broad due, to the complex and varied etiology and pathology of the recited diseases. Therefore, based on the discussions above concerning the art's recognition that liver diseases have multiple causes and that there is no consensus of the role of IL-6 even in the case on Con-A induced hepatitis, the specification fails to teach the skilled artisan how to use the claimed methods without resorting to undue experimentation to diagnose any disease and to treat any disease other than fulminant hepatitis in a mouse model.

Claims 1, 10-15, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim (s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to fusion protein comprising a fragment of a polypeptide of SEQ ID NOs: 16, 20, 22, or 26 fused to a heterologous polypeptide or to polypeptides that are the functional equivalent of or are homologous to polypeptides of SEQ ID NOs: 16, 20, 22, or 26. The claims do not require that the polypeptide or fragment thereof

possess any particular conserved structure, or other disclosed distinguishing feature. The claims do not require any specific percent homology to the sequences of SEQ ID NOs: 16, 20, 22, or 26. Thus, the claims are drawn to a genus of proteins homologous to polypeptides of SEQ ID NOs: 16, 20, 22, or 26 defined as functional equivalents or homologues or to a genus of fusion proteins comprising fragments of SEQ ID NOs: 16, 20, 22, or 26 that have the activity of an antagonist of cytokine expression and/or secretion.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. In this case, the only factor present in the claim is a vague recitation of fragment of a polypeptide, functional equivalence or undisclosed homology. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more that a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NOs: 16, 20, 22, or 26 and fusion proteins comprising the full length sequence of SEQ ID NOs: 16, 20, 22, or 26 fused to a heterologous polypeptide but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

Applicants' traverse this rejection as applied to claims 10-16, 20 and 21 (Response of 13 April 2006, page 16, paragraphs 4-6). The reasons for the traversal are that the specification provides detailed guidance as to how to make and use fragments and the specification discloses that functionally equivalent polypeptides can be identified using the Inpharmatica Gene Threader.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons.

As stated in the rejection, Written Description and Enablement are different issues. There is no conception of molecules commensurate in scope with the claims. A hunting license is not a description of the kill.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application

by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The rejection of Claims 1, 10-15, 20, and 21 under 35 U.S.C. 102(a) and (e) as being anticipated by Baughn, *et al* (WO0240671, publication date 23 May 2002, priority claimed to provisional application 60/249,645, 16 November 2000, cited in previous Office Action) is maintained for reasons of record and for reasons set forth below.

Claim 1 is drawn to polypeptides of SEQ ID NOs:16, 26, 20 or 22 or functional equivalents that are homologous to SEQ ID NOs:16, 26, 20 or 22. Baughn et al. teach a polypeptide, identified as IGSFP-4 which is 100% identical to amino acids 1-240 of SEQ ID NO:20 and comprises a polypeptide (amino acid residues 34-240) which is 100% identical to SEQ ID NO:22 (see enclosed alignments). Absent evidence to the contrary, proteins that comprise sequences that are 100% identical to the sequences of SEQ ID NOs:20 and 22 would be functional equivalents of SEQ ID NOs:20 and 22. The reference teaches an isolated antibody (ligand) which specifically binds to the disclosed polypeptide (page 7, last paragraph), and teach preparation of antibody by immunizing an animal (preparing a natural ligand) (page 14, 2nd paragraph). Thus, the limitations of claims 1, 10-14 are anticipated. The reference teaches that IGFSP plays a role in immune disorders and may be administered to treat a number of diseases, including auto-immune and inflammatory diseases (page 42, 2nd and 3rd paragraphs), thereby anticipating the limitations of claims 15 and 21. Baughn et al teach the administration of an antagonist to treat a subject with an immune disorder; an antibody which specifically binds IGFSP may be used directly as an antagonist. Thus, the limitations of claim 20 is anticipated. Therefore, the teachings of Baughn et al anticipate all the limitations of claims 1, 10-15, 20, and 21.

Applicants traverse this rejection (response of 13 April 2006, page 17, Section V). The reasons for the traversal are that

a. Baughn et al fails to contain all the elements of any portion of the claim (parts i-iv)

b. Baughn does not disclose the existence of an extracellular domain in the IGSFP-4 polypeptide

c. Baughn does not disclose fusing of fragments of the IGFSP protein to heterologous protein

d. Baughn et al. does not provide detailed functional annotation of the IGFSP-4 protein.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons.

In response to argument a and c: The Office has met its burden by citing art that anticipates the limitations of any one of the portions of claim 1; the art does not have to anticipate all of the portions (i-iv) of claim 1. The sequence disclosed by Baughn et al (IGFSP-4) comprises SEQ ID NOs:20 or 22 of the instant invention. Therefore, the protein taught by Baughn et al. is considered to be a functional equivalent of the proteins of SEQ ID NOs 20 or 22.

In response to argument b: Applicants are arguing limitations not in the claims. The claims recite the sequences by SEQ ID NOs; they do not require that the sequence be an extracellular domain.

In response to argument d: While the teachings of Baughn et al do not specifically identify IGFSP-4 as a cytokine antagonist, case law has established that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Also, case law has established that a compound and all of its properties are inseparable, as are its processes and yields (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Absent evidence to the contrary, a protein that comprises an amino acid sequence of 100% homology to that of SEQ ID NO:20 or 22 would have the same or equivalent functional activity; namely, it would function as a cytokine antagonist.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baughn, et al as applied to claim 1 in view of Ruben et al. (2002. US 6,420,526, filed 8 September 1998, the '526 patent). The teachings of Baughn et al. are outlined in detail above. Baughn et al. does not teach a fusion protein which is a fusion protein comprising a fragment which comprises or consists of the amino acid sequence as recited in SEQ ID NO:20 or in SEQ ID NO:22 fused to a heterologous polypeptide. The '526 patent teaches a protein encoded by Gene No:85, whose translation product shares sequence homology with the immunoglobulin superfamily of proteins (Column 77, lines 60-64); the polypeptides taught by Baughn et al are members of the same protein family. The '526 patent teaches that the polypeptide may be used to generate fusion proteins (column 203, lines 58-60). Fusion proteins may be engineered to improve characteristics of the polypeptide: for example, to improve stability (column 204, lines 10-12), increase half-life in vivo (column 204, lines 21-49). Among the fusion proteins taught, are polypeptides combined with parts of the constant domain of

immunoglobulins resulting in chimeric polypeptides which show an increased half-life *in vivo* (column 204, lines 18-23).

Thus, it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Baughn et al and combine the immunoglobulin superfamily proteins taught by Baughn with the constant domain of IgG (as taught by the '526 patent) to obtain chimeric polypeptides. The person of ordinary skill in the art would have been motivated to make this modification because the '526 patent teaches that these fusion proteins show an increased half-life *in vivo*, and would thus be advantageous in therapeutic administration. One would have expected success because making fusion proteins is well known in the art and is taught by the '526 patent.

Conclusion:

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

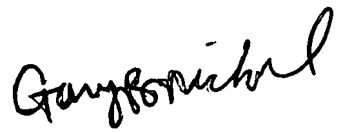
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHS



GARY B. NICKOL, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600